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Committee to Advise on Tropical Medicine and Travel (CATMAT)*

TUBERCULOSIS SCREENING AND THE INTERNATIONAL TRAVELLER

Introduction

Tuberculosis (TB) is a severe and potentially life-threatening disease. The number of new cases of TB are increasing for many reasons in both developed and developing nations. Some international travellers may be at risk of acquiring a new TB infection abroad due to the nature of their travel. Early detection and intervention may have significant health benefits for the individual infected as well as for public health. This paper discusses the rationale for tuberculin skin-test (TST) screening as part of a surveillance program to detect new infections in international travellers. Recommendations are made using evidence-based medicine categories for the strength of the recommendation and the quality of evidence on which the recommendation is made[1].

TB remains the leading cause of death in the world from a single infectious disease[2]. An estimated 8 million new cases of TB infection and 2.9 million deaths occur annually[3]. Approximately one-third of the world's population is infected with *Mycobacterium tuberculosis* and is at risk for developing the disease.

The overall annual risk of TB infection in sub-Saharan Africa is estimated to be 1.5 to 2.5%[2]. In parts of India and other Asian countries the rate of TB also exceeds 100/100,000 population (Figure 1)[4,5]. Recent reports on global TB notification rates indicate a deterioration in control in many parts of the world. They also suggest that significant underreporting may be occurring, particularly in parts of Asia.

These global trends of increasing TB notifications compare poorly to the rates of the disease reported in Canada, which have steadily fallen from 12.1/100,000 population in the early 1980s to a stable rate of approximately 7.5/100,000 population over the last 5 years ending with 1992[6]. The rate of new cases in some regions of the developing world exceeds the rate in Canada by over 300 times.

Not all developed nations have shown a decline in the rate of reported new cases of TB. Switzerland, Italy and the United States are all experiencing a resurgence of new cases[7,8]. Several factors are contributing to this resurgence, including the phasing-out of TB surveillance and control programs, the emergence of multiple-drug resistant TB (MDR-TB), large scale migration, social and natural disasters, and infection with the human immunodeficiency virus (HIV).

The risk of developing clinical TB in tuberculin-positive individuals is very high in HIV-seropositive patients. The rate is estimated to be 7.9 cases per 100 person years (7.9% per year)[9]. Other medical conditions are also associated with an increased risk of developing TB (if infected with *M. tuberculosis*) — sarcoidosis, diabetes, end-stage renal disease, intravenous drug (IVD) abuse, Hodgkin's disease, malignant lymphomas, cancers of the head and neck, gastrectomy, jejunoileal bypass, and being 10% or more below ideal body weight[10].

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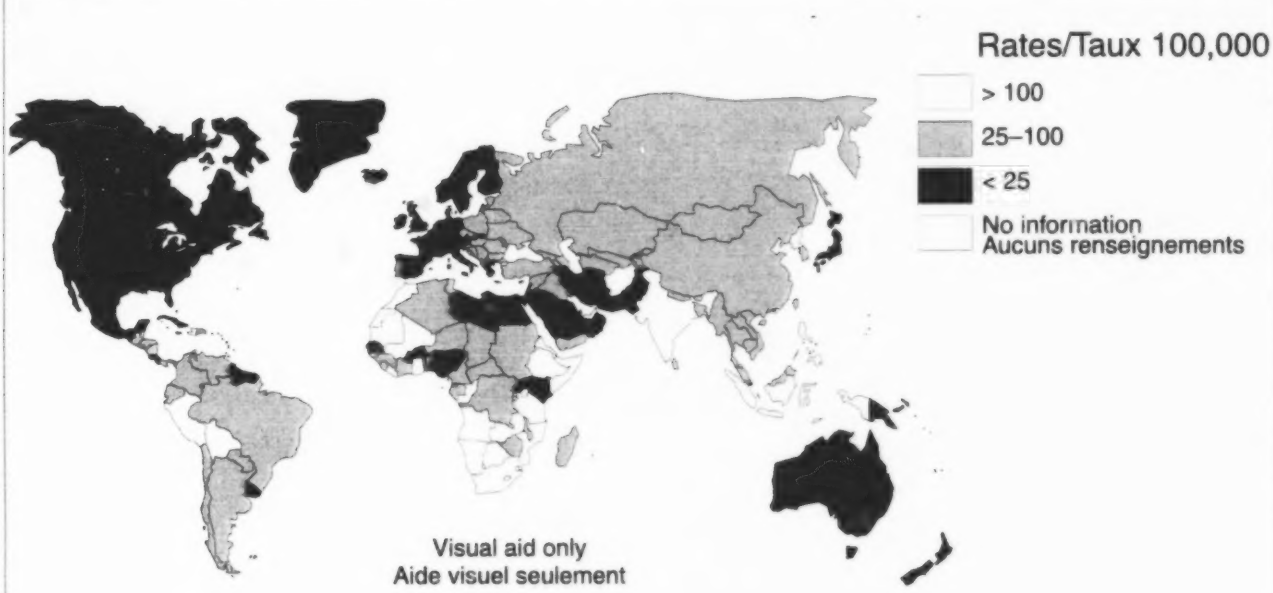
Figure 1
Global Incidence of Tuberculosis[4]



International travel to an area of endemic transmission for TB may be a risk factor for acquiring a new infection[4,5]. However, travel as a risk factor for acquisition of TB is not systematically recorded and reported in epidemiologic records. From preliminary data on 379 prospectively screened travellers who spent at least 1 month in a meso-endemic to hyper-endemic TB transmission zone, six of 47 of these travellers who had completed pre-travel and post-travel screening were diagnosed as having new TB infections. Two of the six travellers were found to actually have TB (Dr. D. MacPherson, Regional Parasitology Laboratory, Hamilton: personal communication, 1996). This suggests that the nature of exposure to TB in Canadians travelling to certain areas abroad may entail as great a risk of infection as that which occurs in the local population. In this study, it is notable that two of the infections occurred in travellers with only 1 month of exposure while abroad.

Due to the mode of transmission of TB (respiratory droplet), it can be assumed that certain travellers may be at risk. Travel in an area of high endemicity; prolonged duration of exposure; and activities which intensify exposure, such as health-care work, refugee-care work, and back packing may be significant in determining acquisition of a new infection. In addition, the presence of any one of several medical conditions mentioned above may predispose the traveller to TB when infection occurs[10].

Once infected with *M. tuberculosis*, there is a risk of developing TB. In a review of the British Medical Research Council's tuberculosis vaccine trials, Styblo estimated the risk of developing TB in recent converters to TST[11]. Of 32,282 participants who were tuberculin-negative [to 100 tuberculin units (TU)] and who had a normal chest x-ray on entry, 12,867 were chosen at random and left unvaccinated. These individuals, nearly all aged 14 to 15.5 years, were followed by periodic TSTs and chest x-rays for about 10 years and cases of TB occurring were recorded for a total of 20 years. Using the criterion of 8 mm of induration or more to 3 TU, 1,335 (10.4%) were found to be infected during an interval of about 10 years and 108 cases of clinical TB had developed during the 10 years following primary infection. A review of the chest x-rays found a total of 234 cases of TB within 15 years of entry among the participants who were initially tuberculin-negative. Fifty-four percent of the cases of TB developed within 1 year, and 80% within 2 years following infection. This indicates that the TST can be a powerful epidemiologic tool to detect who has acquired TB infection and to predict who will be at early risk of disease following tuberculin conversion.

Five units of purified protein derivative (PPD) administered intracutaneously by the Mantoux technique is the recommended method of tuberculin testing. Other strengths of PPD and their interpretation have not been standardized. Induration is then measured 48 to 72 hours later. See Table 1 for interpretative standards for PPD testing[10,12,13]. The surrounding erythema is not used in interpreting the test result. While it is true that the majority of patients with TB will have >10 mm of induration in reaction to 5 TU of PPD (median induration approximately 16-17 mm), it is also true that the majority of persons who have not been exposed to

M. tuberculosis will experience no or very little induration with TST[14].

Table 1
Interpretative Standards for the TST
(Adapted from B. Miller and the American Thoracic Society)

A tuberculin reaction of ≥ 5 mm is classified as positive in the following groups:

- persons who have had close, recent contact with a patient with infectious TB;
- persons who have had a chest x-ray showing fibrotic lesions, which probably indicate previous TB infection;
- persons with HIV infection or with risk factors for HIV infection but in whom the serologic status is unknown; and
- pediatric populations.

A tuberculin reaction of ≥ 10 mm is classified as positive in all other persons who do not meet the above criteria. This would include the following:

- foreign-born persons from high-prevalence countries;
- IVD users;
- low-income populations with restricted access to medical care;
- residents of long-term care facilities;
- persons with pre-existing medical conditions reported to have an increased risk of TB (silicosis, gastrectomy, jejunoileal bypass, being 10% or more below ideal body weight, chronic renal failure, diabetes mellitus, high-dose corticosteroid and immunosuppressive therapy, some hematologic disorders [lymphoma and leukemia] and other malignancies); and
- other high-risk populations identified as geographically or sociodemographically to have a higher prevalence of TB than that found in the general population.

Factors Influencing The Tuberculin Test Result

A. Technique

The tuberculin dose (PPD 5 TU in 0.1 mL) must be delivered intradermally on the volar aspect of the arm using a disposable 1 mL syringe and a 27 gauge needle[15,16]. A wheal must be raised by the injection. If this does not happen then the test should be repeated. Tests are then read 48 to 72 hours later by measuring the transverse diameter of the resulting induration by the technique described by Sokal: a line is drawn with a medium ball-point pen from a point 1 to 2 cm away from the margin of the skin test reaction, toward its center. Moderate pressure is exerted against the skin, and the pen is moved slowly. When the subject's skin turgor is reduced, it is desirable to maintain tension in the skin by exerting slight traction opposite to the direction of the pen movement, from a point behind the pen. When the ball point reaches the margin of the indurated area, and definite resistance to further movement is noted, the pen is then lifted. This procedure is then repeated from the opposite side of the reaction. The lines drawn by the pen provide a visible record of the margins of induration, and the distance between opposing lines can be measured accurately[17].

Two recent reports have raised concerns about the reliability of two tuberculin products used in skin testing IVD users, some of whom were infected with the HIV, and in individuals with no known medical conditions that would predispose to TB[18,19]. Caution is recommended in choosing which tuberculin agent is used for testing and in interpreting the results, especially in high-risk populations.

B. Boosting

Thompson and colleagues described the phenomenon of boosting in health-care givers[16]. This occurs when a previously TB-infected individual demonstrates a negative tuberculin test on initial testing, but a positive result when testing is repeated 1 week or more later. Presumably, the first tuberculin test has boosted an amnestic immune response resulting in an increase in induration by at least 6 mm over the first test, to a total swelling of at least 10 mm. In their study population, boosting was seen in all age groups, but increased with age. Two-step TST should be considered when screening any individual who may have been previously infected with TB and whose initial test is negative.

Since this original description of boosting phenomenon was reported, two Canadian studies have described the same effect in 5.2% of students entering medical training in Montreal, Quebec[20], and in 4.9% of elementary school students in a contact-tracing program in Scarborough, Ontario[21]. This suggests that, although boosting may increase with age and other risk factors for mycobacterial exposure, it is also reasonably common in a young, "low-risk" population.

C. Bacillus Calmette-Guérin (BCG) Immunization

It has been widely held that previous immunization with BCG causes a persistent positive TST[23,24] that can be detected using the boosting technique of Thompson[16]. Some recent studies suggest that positive skin reactions in people previously immunized with BCG are in actual fact due to infection with *M. tuberculosis*[25,26]. Controversy on the effect of BCG immunization on the TST has been reviewed recently[27]. TST is not contraindicated in an individual previously immunized with BCG. In a person who has received BCG, the probability that a positive TST (≥ 10 mm induration) is caused by infection due to *M. tuberculosis* increases with the size of the induration, particularly when the patient is a contact of a person with TB (especially a contagious case when secondary spread has already been documented), when there is a family history of TB or if the patient's country of origin has a high prevalence of TB, and as the interval between BCG immunization and TST increases since BCG reactions wane with time and are not likely to persist beyond 10 years[19,27].

Intervention In Recent Tuberculin Skin Converters

Early detection of conversion to tuberculin positivity is an effective way of predicting who will be at risk of developing TB in the next few years (approximate risk 5% to 8%)[10]. This assumes that with early detection of infection that chemosuppressive therapy will be effective in preventing TB. In several studies using isoniazid (INH) preventive therapy protective efficacy ranging from 54% to 93% is reported[10]. The greater efficacy was seen in patients who were most compliant with therapy. In a long-term follow-up study, the protection produced by INH persisted for more than 19 years[26]. The authors suggested that the decrease in TB risk produced by INH was lifelong.

Adverse drug events (especially INH hepatitis)[28-30] and MDRTB[31-34] may significantly reduce the value this approach has in preventing TB. The individual's potential benefit from INH versus the risk of adverse drug reactions, including death, must be carefully considered when recommending chemosuppresive therapy[35].

Summary Recommendations

1. Travellers who have not had a previous documented positive PPD nor a history of TB and are at high risk of exposure to TB due to travel in a high-endemic environment (Figure 1), have a medical condition increasing the risk of TB, have "high-risk" lengths of travel or, participate in high-risk activities leading to probable exposure should have a pre-exposure TST. (BIII)[2,4,5,10]

   Currently, no published data defines "high-risk" lengths of travel, but estimates of TB acquisition rates in sub-Saharan Africa and parts of Asia, in combination with other risk factors, would support pre-travel and post-travel screening for durations of exposure > 1 month. (BII)

2. Post-exposure TST, or testing at least every 2 years, should be done for all tuberculin-negative reactors. (AI)[11]

3. Two-step TST should be considered in all individuals who are negative on the initial test and who may have an amnestic response to previous *M. tuberculosis* exposure. (AII)[16]

   This group would include health-care workers, individuals who were born and grew up in a TB-endemic area, and people who have a history of possible exposure to TB. In practice, anyone who has had a negative PPD within 5 years and is immune competent, will require only one PPD test prior to travelling.

4. Recent tuberculin skin convertors (within 2 years) are at greatest risk of developing TB and should be considered for chemosuppressive therapy. (AII)[4,5,11,12,25]

5. In some cases, due to increasing MDR-TB, the risk of INH may exceed its benefit in a recent tuberculin converter. (AII)[26]

   A careful review of the clinical indications and the recent data on drug resistance should be done prior to prescribing INH. Alternative chemosuppressive agents may need to be considered. In some cases, a specialist in infectious diseases, tropical medicine or a respirologist should be consulted.

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SURVEY OF VANCOMYCIN-RESISTANT ENTEROCOCCI IN THE FRASER VALLEY OF BRITISH COLUMBIA

Vancomycin susceptibility testing was performed on 305 clinical isolates of enterococci collected at random from all types of specimens from both inpatients and outpatients between February and May 1996 from 12 hospitals in the Fraser Valley of British Columbia.

The identification of enterococci was based on conventional biochemical methods. All 305 isolates were subcultured to bile-esculin azide agar (BEA) and BEA supplemented with 6 mg/L of vancomycin (BEAV). Six of the 305 enterococcal isolates grew on BEAV and underwent further vancomycin susceptibility testing by E-test (AB biodisk) and Kirby-Bauer disk diffusion (NCCLS standards).

The four isolates of *Enterococcus faecalis* grew on BEAV but were susceptible to vancomycin by disk diffusion and E-test with MICs between 2 and 4 mg/L. Two isolates of *E. casseliflavus* grew on BEAV and demonstrated low-level vancomycin resistance by E-test with MICs of 8 and 12 mg/L respectively. Vancomycin resistance was not detected by disk diffusion for these two isolates.

Although the results of the study demonstrate that high-level vancomycin resistant enterococci (VRE) do not exist in the Fraser Valley, surveillance is continuing. Routine screening cultures are now being done for VRE in area hospitals on those patients who were recently admitted to health-care facilities outside the province of British Columbia.

Source: *A Lau, ART, Laboratory Scientist, Fraser Valley Regional Laboratory Services, J Roy, MD, Microbiologist; C Wong, MD, Infectious Diseases, Royal Columbian Hospital, New Westminster; A Skidmore, MD, Microbiologist, Surrey Memorial Hospital, J Tomblin, MD, Microbiologist, Peace Arch District Hospital, White Rock; S Henwick, MD, Matsqui-Sumas-Abbottsford Hospital, Abbotsford, British Columbia.*

Editorial Comment

As indicated in the 1 August issue of CCDR, VRE are emerging as important nosocomial pathogens in Canada. The hospitals in the Fraser Valley are, as are many health care facilities across Canada, responding proactively to this threat by initiating ongoing surveillance for VRE in selected patients. The Canadian Nosocomial Infection Surveillance Program is actively developing an ongoing program to track the emergence and spread of VRE in Canada. In addition, *Guidelines for Preventing the Spread of VancomycinResistant Enterococcus in Canada* are currently being developed and should be available in draft form in the fall of 1996.

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